REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.116, are respectfully requested.

By the foregoing amendment, claims 33-35, 37, 59-61, 63, 66-68 have been canceled without prejudice or disclaimer of the subject matter recited therein. Applicants reserve the right to file a continuation or divisional application directed to any subject matter deleted by way of this Amendment.

Further, claims 32, 43, 44, 52, 65, 74 and 78 have been amended to further clarify Applicants' invention. Support for the amendments can be found throughout the specification and claims as-filed, especially on page 8, line 2, page 14, lines 32-33 and claims 35, 61 and 68. Accordingly, no new matter has been added.

I. Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 32-38, 40, 43, 44, 46-47, 52-58, 65-72 and 74-80 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse this rejection.

Specifically, the Office Action asserts that while claims 32, 44, and 65 use the phrase "consisting of", the composition of dependent claims 43, 52 and 78 use the term "comprises". Further, the Office Action states that the claims are indefinite because the composition also comprise one or more vectors which express the

specified papillomavirus polypeptides, and so it purportedly cannot be determined what is included in the composition.

In the interest of expediting prosecution and without ceding to the rejections cited in the Office Action, claims 32, 44, and 65 have been amended herein to recite "a" instead of "one or more" when referring to the recombinant vectors. Moreover, to bring the scope of the dependent claims in line with the base claims, the wording of claims 43, 52 and 78 has been amended herein to recite "wherein said recombinant MVA vector is provided in combination with a pharmaceutical acceptable carrier", instead of "further comprising a pharmaceutical acceptable carrier".

Therefore, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 112, second paragraph.

II. Rejections Under 35 U.S.C. § 102

Claims 32-34, 40, 43, 53 and 54 stand rejected under § 102(e) as allegedly anticipated by Stanley (U.S. Patent No. 6,096,869). Applicants respectfully traverse this rejection.

To be anticipating, a reference must disclose each and every element of the claimed invention. *SSIH Equipment v. U.S. International Trade Comm.*, 218 USPQ 678, 688 (Fed. Cir. 1983). Applicants submit that the cited reference fails to recite each and every element of the claims, as amended herein.

The Office Action argues that although claims recite a composition "consisting of" the recited elements, the ingredients of the composition are indefinite because

the composition may "further comprises" additional ingredients in dependent claims. On this basis, the Office Action asserts that the composition of Stanley anticipates the instant claims, even though the composition of Stanley does not disclose the specific combination of papillomavirus and immunostimulatory polypeptides recited in the instant claims.

As previously discussed, claims 32, 44, 65 have been amended herein to recite "a" instead of "one or more" when referring to the recombinant vectors. Moreover, claims 43, 52 and 78 have been amended herein to recite "wherein said recombinant MVA vector is provided in combination with a pharmaceutical acceptable carrier", instead of "further comprising a pharmaceutical acceptable carrier". Applicants submit that these amendments overcome the present rejection. The newly amended claims are drawn to a composition "consisting of" only the elements recited in the claims, *i.e.* a recombinant vector expressing the specified papillomavirus polypeptides, and thus exclude the inclusion of other ingredients. Thus, Applicants submit that Stanley is no longer relevant to the claimed invention.

Therefore, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 102(e).

VI. Rejections Under 35 U.S.C. § 103(a)

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. The Examiner can satisfy this burden by showing, first, that the cited prior art

coupled with the general knowledge at the time of the invention must contain some suggestion or incentive to motivate a skilled artisan to modify or combine references. *See In re Fine,* 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988); *In re Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986). Second, the Examiner must show that the modification or combination of prior art references must have a reasonable expectation of success (at the time of the invention). *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). Lastly, the Examiner must show that the cited or combined references teach each and every limitation of the claims. *See In re Zurko,* 111 F.3d 887, 888-89, 42 U.S.P.Q.2d 1476, 1478 (Fed. Cir. 1997); *In re Wilson,* 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). Applicants submit that a case of obviousness has not been adduced. The rejections are specifically addressed below.

Claims 32-36, 43 and 53-56 stand rejected under 35 USC § 103 (a), as allegedly being unpatentable over Galloway, Borysiewicz *et al.*, and Lin *et al.*

Borysiewicz *et al.* disclose a recombinant Wyeth vaccinia virus expressing the E6 and E7 polypeptides of human papillomavirus types 16 and 18 (TA-HPV). More specifically, TA-HPV carries two expression cassettes, each encoding an E6/E7 fusion polypeptide for both HPV-16 and HPV-18, in which the E6 termination codon was altered to place the E6 open reading frame in frame with that of E7. The HPV-16 E6/E7 and the HPV-18 E6/E7 fusion genes are placed under the control of the

7.5K and H6 promoters respectively and inserted at a neutral site in the vaccinia virus Wyeth strain genome. A phase I vaccination studies was conducted in patients with invasive cervical cancer. Following administration of TA-HPV, study participants developed antibody responses both to the vaccinia virus and the inserted HPV sequence.

Lin *et al.* disclose vector constructs expressing one of the CRPV capsid polypeptide, respectively a WR vaccinia virus encoding the L1 late protein under the control of the 7.5K promoter (*see* page 613) or plasmids encoding either a trpE-L1 or a trpE-L2 fusion protein (*see* 614). The protection of rabbits against CRPV infection was first evaluated after administration of crude trpE-L1 or trpE-L2 fusion proteins (four injections given at 3 weeks intervals). Experimental data showed that immunization with either of the structural proteins completely protected rabbits from CRPV challenge. In a second approach, protection of rabbits provided by the recombinant L1-expressing vaccinia vector was evaluated after primary vaccination (intradermally injections at multiple sites) followed by a booster 1 month later with the same dose of virus. L1-VV vaccinated rabbits developed a strong antibody response and were protected against CRPV infection.

Galloway disclose a number of preclinical studies conducted in various animal models with either late or early papillomavirus polypeptides produced from virus extract or by recombinant technology (*see* on pages 190-191). In the vast majority, administration of the late polypeptides protected vaccinated animals against virus challenge. With respect to early papillomavirus polypeptides, a

recombinant vaccinia virus expressing the BPV E5, E6 or E7 genes could retard the development of tumors resulting from challenge with a BPV-transformed cell line in syngenic rats. On the basis of the results obtained with vaccines against animal papillomavirus, Galloway hypothesizes about potential treatments for HPV infections.

Thus, Lin *et al.* disclose a composition consisting of a lytic WR vaccinia virus encoding the L1 late protein, which provides protection against CRPV challenge. There is no suggestion to express both L1 and L2 polypeptides in the same vaccinia vector, and furthermore to express E6 and E7 polypeptides to additionally provide a therapeutic effect. Borysiewicz *et al.* disclose a composition consisting of a lytic Wyeth vaccinia virus expressing HPV-16 early E6 and E7 polypeptides, which administration elicits antibody response in patients with cervical carcinomas. This reference does not teach or suggest the expression of L1 and L2 polypeptides in the same vaccinia vector to additionally provide a prophylactic effect. Galloway does not remedy the deficiencies of either Lin *et al.* or Borysiewicz *et al.*, because this reference likewise neither teach nor suggest a vector-based co-expressing the late L1 and L2 capsid polypeptides together with the E6 and E7 oncoproteins.

The Office Action asserts that one of ordinary skill in the art at the time the invention was made would have been motivated to express L1 and L2 in the vaccinia vector of Borysiewicz *et al.*, or E6 and E7 in the vaccinia vector of Lin *et al.* The Office Action argues that one would have been motivated to combine the polypeptides into one composition and to administer the same composition to those

who need treatment and those who need protection. Further, the Office Action argues that one of ordinary skill in the art would have had a reasonable expectation of producing the composition of the invention because the composition of Borysiewicz *et al.* purportedly treats infected patients and the composition of Lin *et al.* purportedly prevents disease.

In the interest of expediting prosecution, the claims have been amended herein to recite a recombinant MVA vector, expressing independently the recited polypeptides. The claims now recite a composition consisting of a recombinant MVA vector expressing the early E6 and E7 and the late L1 and L2 papillomavirus polypeptides, each of the expressed sequences being under the control of the appropriate elements for its expression in a host cell or organism.

Thus, Applicants submit that the assertion in the Office Action that the skilled artisan would have been motivated to combine the polypeptides into one composition, especially in view of Galloway teaching that the late polypeptides are prophylactic and the early polypeptides are therapeutic, goes beyond actual teaching in the art. Indeed, if Galloway hypothesizes that the late polypeptides are prophylactic and the early polypeptides are therapeutic, this reference likewise does not suggest the possibility of combining in the same composition both late and early polypeptides to provide both therapeutic and prophylactic effects. Galloway uses the term "or" and does not report any preclinical studies which support such a combination. Rather, Galloway provides a very general discourse on HPV therapies, which points out that the HPV late polypeptides might be expected to

provide a prophylactic effect and the HPV early polypeptides might be expected to provide a therapeutic effect. The hypothetical nature of Galloway's comments is evident from the text. "It should be feasible to develop prophylactic vaccines to prevent HPV infection using the L1 and L2 capsid proteins **or** therapeutic vaccines to modulate the development or recurrence of disease based on the E6 and E7 oncoproteins or other viral proteins." (*see* abstract). Further, Galloway states "However, it is difficult to provide evidence of the efficacy of HPV vaccines because of the inability to propagate the virus in culture or in animal models and because of the incomplete understanding of the natural history of HPV infection".

A reasonable expectation of success must be founded in the cited references in order for a case of obviousness to be adduced. In the instant case, Applicants submit that the Examiner's interpretation is founded in the disclosure of the present application. As it is evident from the hypothetical language employed and the difficulties raised in connection with HPV, Galloway fails to provide a reasonable expectation of success to one of ordinary skill in the art.

Moreover, the co-expression of both the late L1 and L2 polypeptides and the early E6 and E7 polypeptides by a recombinant vector (such as a recombinant MVA vaccinia virus) ensures that they are delivered together at the same time and at the same site, giving an improved immune response to the four papillomavirus polypeptides. This can be expected to lead to an elevation and acceleration of response to the vector components of the composition. There is of course, no teaching in any of the cited references, either individually or in combination, of the

advantages which might be obtained by co-expression of the four papillomavirus polypeptides in a recombinant vector composition of the type claimed in the present claims.

Thus, there is nothing in the cited publications which would motivate one of ordinary skill in the art to arrive at the present invention. There is no suggestion that a recombinant vector could be constructed with four expression cassettes, each expressing the individual papillomavirus polypeptides. In the instant case, the references teach expression of a single polypeptide (*e.g.* a WR vaccinia virus encoding the L1 late protein as disclosed by Lin *et al.*) or two early polypeptides modified so as to form a fusion polypeptide (*e.g.* a Wyeth vaccinia virus encoding an E6/E7 fusion polypeptide as disclosed by Borysiewicz *et al.*).

Claims 44, 46, 48, 52, 59-62, 65-69, 72, 74, 78-80 stand rejected under 35 USC § 103 (a), as allegedly being unpatentable over Stanley *et al.*, Galloway, Borysiewicz *et al.*, and Lin *et al.* as applied above and further in view of Hines *et al.*

The Office Action asserts that Hines *et al.* establish that cytokine, *i.e.* IL-2, activates cytotoxic T cells. The Office Action continues to assert that one of ordinary skill in the art at the time the invention was made would have been motivated to express IL-2 of Hines *et al.* in the vaccinia vector of Borysiewicz *et al.* and of Lin *et al.*, to stimulate a cellular immune response against papillomavirus tumor formation *in vivo*. The Office Action asserts that substituting one cytokine for another in the vaccinia vector composition of Stanley *et al.* or expressing the cytokine in the

vaccinia vector of Borysiewicz *et al.* and of Lin *et al.* would be obvious to one of ordinary skill in the art, without unexpected results. The Office Action asserts that the combination of references purportedly not only teach all of the required elements in the claims, but also demonstrate several motivating factors for combining the teachings to produce success once combined.

Again, Applicants respectfully note that a proper analysis under 35 USC § 103 requires consideration of whether the cited references would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process, and whether the cited references would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. In the instant case, the cited references meet neither of these factors.

Stanley *et al.* disclose the combination of IL-12 with one or more papillomavirus polypeptides. In the instant case, Applicants have discovered that by administering a vector co-expressing (i) an immunostimulatory polypeptide selected from the group consisting of IL-2, IL-7, the co-adhesion molecule B7.1 and the co-adhesion molecule B7.2 and (ii) specified papillomavirus polypeptides, the growth of HPV-induced tumoral lesions may be inhibited. Stanley *et al.* does not teach or suggest such combination. In fact, Stanley *et al.* teaches away from a combination involving non-IL-12 immunostimulatory polypeptides.

Applicants note that the Office Action quotes the description in Stanley *et al.* of IL-12 and its biological role as a cytotoxic lymphocyte maturation factor, to argue

that Stanley *et al.* teaches the importance of administering a cytokine to stimulate T cells in order to reduce HPV-induced tumors. Applicants submit that the Office Action has in fact broadened the disclosure of Stanley *et al.* to encompass the possibility of using any cytokine in the treatment of papillomavirus-associated conditions. There is no exemplification or even a suggestion in Stanley *et al.* that non-IL-12 cytokine would achieve a similar clinical effect.

In fact, Applicants draw the Examiner's attention to the fact that Stanley *et al.* recognizes that non IL-12 cytokines do not play any role in HPV-induced tumors regression as indicated column 2 lines 48-51 of U.S. Patent No. 6,096,869, which states "The present invention arises from a surprising finding that IL-12 is present in 100% of regressing HPV-induced tumors surveyed by the present inventors in a clinical study –unlike many other cytokines also surveyed". Further, the experimental data clearly establish that IL-2 expression is quite different from IL-12 expression in the different categories of cervical biopsies analyzed in this study. Indeed, in marked contrast to IL-12, IL-2 transcripts are detected in normal cervix (table e), as well as in some of the non-regressing lesions (*see* 5/8 in table c, 2/7 in table b).

Thus, Applicants again note that the disclosure of Stanley *et al.* is limited to the use of IL-12 in combination with one or more papillomavirus polypeptides (more than 80 possible combinations) for treating HPV-induced conditions. There is no suggestion in the Stanley reference to combine HPV polypeptides with non-IL-12

cytokines. On the contrary, Stanley *et al.* experimentally demonstrate that non IL-12 cytokines are not associated with regressing HPV-induced tumors.

Thus, Stanley *et al.* do not provide sufficient guidance to suggest a reasonable expectation of success when expressing immunostimulatory polypeptides other than IL-12 (*e.g.* IL-2, IL-7, B7.1 and B7.2) to treat HPV-induced lesions. Therefore, one of ordinary skill in the art would not be motivated to express a combination of such immunostimulatory molecules with HPV polypeptides to provide immunity and limit the occurrence of HPV-induced cancers.

The remaining references do not remedy the deficiencies of Stanley *et al.*, since these references likewise neither teach nor suggest vector–based composition co-expressing an immunostimulatory polypeptide in combination with the specified papillomavirus polypeptides. As admitted by the Office Action, Borysiewicz *et al.*, Lin *et al.*, and Galloway all fail to disclose or suggest to include an additional expression cassette driving expression of a cytokine in the recombinant vector expressing the papillomavirus polypeptides, in order to improve anti-papilloma immune response. To the contrary, Galloway reports an incomplete understanding of the relationship of papillomaviruses with the immune system (*see* page 191, second paragraph of the first column and second column).

Hines *et al.* describe a cell-mediated gene transfer method referred as "cellular adoptive transfer of stimulated cytotoxic T lymphocytes". The method disclosed by Hines involves obtention of blood lymphocytes from a cancer patient, *in vitro* stimulation with a HPV peptide and IL-2 and reintroduction of the *in vitro*

activated lymphocytes into the cancer patient. As discussed on page 862 of Hines *et al.* " the rational for this [cellular adoptive transfer of stimulated cytotoxic T lymphocytes] is that controlled in vitro stimulation of lymphocytes is more likely to yield effective antitumor responses compared to the response generated by the host in vivo ". Therefore, Hines *et al.* contain no disclosure or even suggestion that the HPV polypeptide and the immonostimulatory polypeptide need to be co-expressed in the same recombinant virus.

In contrast to Hines approach, the present invention does not provide a controlled *in vitro* stimulation of lymphocytes known to be involved in anti-tumor response, but rather relies on a recombinant MVA vector to locally deliver a cytokine and HPV polypeptides. Prior to the present invention, it was not known whether sufficient levels of cytokine and HPV polypeptides could be produced *in situ* so as to provide regression of HPV infection and HPV-induced-tumors. In this regard, it was not known whether the local production of cytokine and HPV polypeptide expressed from a single MVA recombinant vector would be adequate to properly present the HPV antigens and successfully stimulate the host's immune cells. Additionally, it was not known whether over production of the cytokine (e.g. IL-2) might cause a cytotoxic effect, thereby rendering the composition of the present invention unsuitable for such applications.

Moreover, Hines teaches away from the present invention by describing cell-based immunotherapy. The methodology described in this reference differs substantially from the present invention because it involves *in vitro* modification of

cells (i. e. controlled *in vitro* stimulation of T lymphocytes) followed by reimplantation in the host, rather than relying on a recombinant MVA vector to locally deliver an immunostimulatory molecule along with HPV polypeptides.

Claim 47 stands rejected under 35 USC § 103 (a), as allegedly being unpatentable over Stanley *et al.*, Galloway, Borysiewicz *et al.*, Lin *et al.* and Hines *et al.* as discussed above, and further in view of Gajewski.

Gajewski relates to B7.1 and describes its ability to co-stimulate T lymphocytes for IL-2 production and proliferation. Using syngenic mixed lymphocyte-tumor culture, it was shown that B7.1-transfected P815 tumor cells elicited P815 specific CTL activity in the presence of IL-6 and IL-12 and following restimulation along with IL-2 and IL-7 (see Figure 2 and results). On this basis, it is suggested that autologous tumor cells can be *in vitro* modified by B7.1 gene transfection to stimulate CD8+ cells upon reimplantation (see bottom of page 470). It should be noted that Gajewski has failed to demonstrate that any B7.1-transfected autologous tumor cells can be administered *in vivo* and achieve adequate stimulation of CD8 immune cells.

Gajewski simply discloses that cytokines, especially B7.1, can markedly influence the immune response. Once again, because these molecules are so short lived, there are problems associated with delivering these molecules to sites of immune reactivity. However, there is no disclosure or teaching in Gajewski of the essential feature of the present invention, *i.e.*, to express in a single recombinant

MVA vector the HPV polypeptides with the B7.1 cytokine, in order to improve anti-papillomavirus immune response.

Applicants note that Gajewski relies on *in vitro* stimulation of cells, and thus teaches away from the present invention. Indeed, Gajewski's approach differs substantially from the present invention because it involves *in vitro* modification of cells (e.g. B7.1-transfected tumor cells) followed by reimplantation in the host, rather than relying on the use of a vector co-expressing the recited immunostimulatory molecule and HPV polypeptides. Also lacking from Gajewski reference is any reasonable suggestion that such a recombinant vector could locally deliver therapeutically effective amount of B7.1 together with the HPV polypeptides, *i.e.* to successfully provide a therapeutic effect; especially in view of the incomplete understanding of HPV-mediated immune responses, as expressed by Galloway.

Claims 37, 63 and 70 stand rejected under 35 USC § 103 (a) as allegedly unpatentable over Stanley *et al.*, Galloway, Borysiewicz *et al.*, Lin *et al.*, Hines *et al.* and Gajewski as applied above, and further in view of Boursnell *et al.*

Boursnell *et al.* disclose a recombinant vaccinia virus expressing the E6 and E7 polypeptides of human papillomavirus types 16 and 18, wherein the sequences encoding the E6 and E7 polypeptides from both HPV-16 and HPV-18 are fused together to form a single open reading frame. Boursnell *et al.* recommend using the Wyeth strain of the vaccinia virus as this vector had the lowest number of side effect complications (see page 14 lines 17-25). In light of the numerous advantages

provided by the Wyeth strain of the vaccinia virus in connection with human use, Applicants submit that one of ordinary skill in the art at the time the invention was made would not have been motivated to use a MVA vector to express the papillomavirus and the immunostimulatory polypeptides. Indeed, MVA is known to be non lytic and highly attenuated. As known by one skilled in the art, infection provided by either the Wyeth vaccinia virus used in Borysiewicz or the related WR vaccinia virus strain used in Lin's study is lytic. This property is one of the criteria that has contributed to the choice of this vector by Borysiewicz *et al.*, for use in cervical cancer (*see* on page 1526). It is indeed expected that a lytic vector has the ability to enhance the host's immune response as compared to a non lytic vector, due to the degradation of the infected cells. Applicants also draw the Examiner's attention to page 29 line 2-9 of Boursnell, which clearly recommends the use of non attenuated vaccinia vector when an immunotherapy strategy is considered in connection with the treatment of HPV-induced lesions, stating "However, for an immunotherapy strategy,...use of an attenuated virus is considered undesirable since it could compromise the immunological response to the papillomavirus antigens".

Therefore, one of ordinary skill in the art at the time the invention was made would not have been motivated to use a recombinant MVA vaccinia virus vector, known to be non lytic and highly attenuated, in order to treat or reduce papillomavirus-induced lesions.

Claims 38, 64 and 71 stand rejected under 35 USC § 103 (a) as allegedly unpatentable over Stanley *et al.*, Galloway, Borysiewicz *et al.*, Lin *et al.*, Hines *et al.* and Gajewski as applied above, and further in view of Meyer *et al.*

Meyer *et al.* compare the genome of the highly attenuated MVA strain with the ancestral wild type strain. They disclose that six major deletions occurred in the MVA genome during the attenuation process. These alterations are assumed to contribute to the decreased viral virulence and a restricted host range infectivity. However, Meyer *et al.* fail to suggest that a recombinant MVA vector co-expressing the recited papillomavirus polypeptides, and eventually an immunostimulatory molecule could be used to treat HPV-associated lesions. Moreover, as discussed above in connection with Boursnell, one of ordinary skill in the art at the time the invention was made would not have been motivated to use a MVA vector to express *in vivo* the papillomavirus polypeptides and the immunostimulatory polypeptide.

Claims 40, 49-51, 57, 58 and 75-77 stand rejected under 35 USC § 103(a) as allegedly unpatentable over Stanley *et al.*, Galloway, Borysiewicz *et al.*, Lin *et al.*, Hines *et al.* and Gajewski as applied above, and further in view of Crook *et al.* and Munger *et al.*

Crook *et al.* disclose the non oncogenic E6 variant having amino acid deletion of residues 111-115, whereas Munger *et al.* disclose that amino acid residues surrounding the cysteine residue in position 24 are involved in interaction with restinoblastoma tumor suppressor gene product. However, they fail to remedy the

deficiencies of Stanley *et al.*, Galloway, Borysiewicz *et al.*, Lin *et al.*, Hines *et al.* and Gajewski, as discussed in detail above.

Thus, Applicants submit that the presently claimed invention is patentable over the references cited, especially in light of the amendments to the claims and the remarks supplied above. Therefore, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 103(a).

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: _____
Deborah H. Yellin
Registration No. 45,904

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

Date: January 2, 2003

Attachment to Amendment and Reply dated January 2, 2003
Marked-up Claims

32. (Three Times Amended) A composition consisting of a [one or more] recombinant modified Ankara (MVA) vector [vectors] into which are inserted DNA sequences coding for (i) the early E6 polypeptide [and E7 polypeptides] of a papillomavirus; (ii) the early E7 polypepetide of a papillomavirus; (iii) [and DNA sequences coding for] the late L1 polypeptide [and L2 polypeptides] of a papillomavirus; and (iv) the late L2 polypeptide of a papillomavirus; each of said DNA sequences being placed under the control of the elements necessary for its [their] expression in a host cell or organism.

43. (Amended) The composition of claim 32, wherein said recombinant MVA vector is provided in combination with [further comprising] a pharmaceutically acceptable carrier.

44. (Three Times Amended) A composition consisting of a [(i) one or more] recombinant modified Ankara (MVA) vector [vectors] into which are inserted DNA sequences coding for (i) the early E6 polypeptide [and E7 polypeptides] of a papillomavirus; (ii) the early E7 polypepetide of a papillomavirus; (iii) [and DNA sequences coding for] the late L1 polypeptide [and L2 polypeptides] of a papillomavirus; and (iv) the late L2 polypeptide of a papillomavirus; and (v) a [said DNA sequences being placed under the control of the elements necessary for their

expression in a host cell or organism and (ii) one or more recombinant vectors into which is inserted a DNA sequence coding for one] polypeptide having an immunostimulatory activity;

wherein each of said DNA [sequence] sequences is placed under the control of the elements necessary for its expression in a host cell or organism and wherein said polypeptide having an immunostimulatory activity is selected from the group consisting of interleukin-2, interleukin-7, the co-adhesion molecule B7.1 and the co-adhesion molecule B7.2.

52. (Twice Amended) The composition of claim 44, wherein said recombinant MVA vector is provided in combination with [further comprising] a pharmaceutically acceptable carrier.

65. (Twice Amended) A composition consisting of a [one or more] recombinant modified Ankara (MVA) vector [vectors] into which are inserted [(i)] DNA sequences coding for (i) the E6 polypeptide of a papillomavirus [and] (ii) [for] the E7 polypeptide of a papillomavirus and (iii) [(ii) one DNA sequence coding for] a polypeptide having an immunostimulatory activity; each of said DNA sequences being placed under the control of the elements necessary for its [their] expression in a host cell or organism and wherein said polypeptide having an immunostimulatory activity is selected from the group consisting of interleukin-2, interleukin-7, the co-adhesion molecule B7.1 and the co-adhesion molecule B7.2.

78. (Amended) The composition of claim 65, wherein said recombinant MVA vector is provided in combination with [further comprising] a pharmaceutically acceptable carrier.